# Characterization of Coronary Artery Disease in Young Adults and Assessment of Long-term Outcomes

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**ABSTRACT:** **Background:** Contemporary data on clinical profiles and long-term outcomes of young adults with coronary artery disease (CAD) are limited.

**Objectives:** To determine the risk profile, presentation, and outcomes of young adults undergoing coronary angiography.

**Methods:** A retrospective analysis (2000–2017) of patients aged ≤ 35 years undergoing angiography for evaluation and/or treatment of CAD was conducted.

**Results:** Coronary angiography was performed in 108 patients (88% males): 67 acute coronary syndrome (ACS) and 41 non-ACS chest pain syndromes. Risk factors were similar: dyslipidemia (69%), positive family history (64%), smoking (61%), obesity (39%), hypertension (32%), and diabetes (22%). Eight of the ACS patients (12%) and 29 of the non-ACS (71%) had normal coronary arteries without subsequent cardiac events. Of the 71 with angiographic evidence of CAD, long-term outcomes (114 ± 60 months) were similar in ACS compared to non-ACS presentations: revascularization 41% vs. 58%, myocardial infarction 32% vs. 33%, and all-cause death 8.5% vs. 8.3%. Familial hypercholesterolemia (FH) was diagnosed in 25% of those with CAD, with higher rates of myocardial infarction (adjusted hazard ratio [HR] 2.62, 95% confidence interval [95%CI] 1.15–5.99) and revascularization (HR 4.30, 95%CI 2.01–9.18) during follow-up. Only 17% of patients with CAD attained a low-density lipoprotein cholesterol treatment goal < 70 mg/dl.

**Conclusions:** CAD in young adults is associated with marked burden of traditional risk factors and high rates of future adverse cardiac events, regardless of acuity of presentation, especially in patients with FH, emphasizing the importance of detecting cardiovascular risk factors and addressing atherosclerosis at young age.

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**KEY WORDS:** acute coronary syndrome (ACS), coronary artery disease (CAD), familial hypercholesterolemia (FH), young adults

The presence of traditional risk factors in adulthood and a family history of coronary disease at a young age are strong predictive markers for the development of clinical atherosclerosis in midlife [1]. Family history of premature coronary artery disease (CAD) is often defined as an early disease onset in males aged < 55 years and females < 60 years in first-degree relatives. An increase in the rate of clinical CAD is often seen at age 40–45 years, but estimates vary considerably depending on the population studied and their ethnic origin, whereas data on the risk profile and CAD incidence in adults younger than 35 years of age are limited, and cardiac catheterization in this age group is uncommon [2,3]. Moreover, long-term patient follow-up, particularly important at this age, is lacking. Available data are probably outdated due to changing risk profiles for early cardiovascular disease observed in recent decades among adolescents, such as poor diet, physical inactivity, and the increase in incidence of obesity and diabetes. Current data are therefore needed to describe the features, risk profiles, and long-term prognosis associated with CAD in young adults.

Heterozygous familial hypercholesterolemia (FH) is a prevalent monogenic disease associated with premature CAD and reduced life expectancy [4]. FH is significantly underdiagnosed and undertreated in the general population, and the disease is often identified too late, after a first coronary event [4]. Data are lacking regarding the incidence, features, and long-term outcomes of heterozygous FH patients presenting with early CAD. Systematic screening of catheterization laboratory databases was shown to promote diagnosis of high-risk patients with severe FH and enable identification of their affected family members through cascade screening [5].

The aim of the present study was to investigate the clinical profiles and long-term outcomes of young adults referred for coronary angiography for evaluation or treatment of suspected CAD and to examine the burden and clinical implications of FH in this population.

## PATIENTS AND METHODS

### STUDY POPULATION

We retrospectively investigated all patients aged 35 years or younger who were referred for coronary angiography in a single center (Carmel Medical Center, Haifa, Israel) from 2000 to 2017 for evaluation and treatment of CAD. The study population flowchart is presented in Figure 1. Patient characteristics, risk factors, and relevant historical details were gathered from elec-

tronic data files, as was acuity of presentation and angiographic data. Obesity was defined as body mass index > 30 kg/m$^2$. Blood tests that were analyzed were those that were taken during hospitalization or nearest to the index procedure. The clinical diagnosis of FH was established using the Dutch Lipid Clinic Network (DLCN) algorithm [6]. Peak low-density lipoprotein (LDL) cholesterol levels documented in each patient's history was used to calculate the DLCN score. Information on physical findings of lipid accumulation in tissues (arcus cornea and tendon xanthomas) as well as lipid levels and physical findings in first-degree relatives were not available for all patients. Missing information was counted as zero in the DLCN algorithm. FH was considered probable or definite if the total score was ≥ 6 points.

Angiographic CAD was defined as any evidence of atherosclerotic plaque causing at least mild coronary artery stenosis. An acute coronary syndrome (ACS) was categorized according to discharge diagnoses and hospitalization records as unstable angina pectoris (UAP)/non-ST segment elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI). Cardiac outcomes over a mean follow-up period of 114 ± 60 months were analyzed, including revascularization procedures, myocardial infarction, and all-cause death. In addition, most recent LDL cholesterol level of each patient was documented, and attainment rates of lipid treatment goals were accordingly assessed.

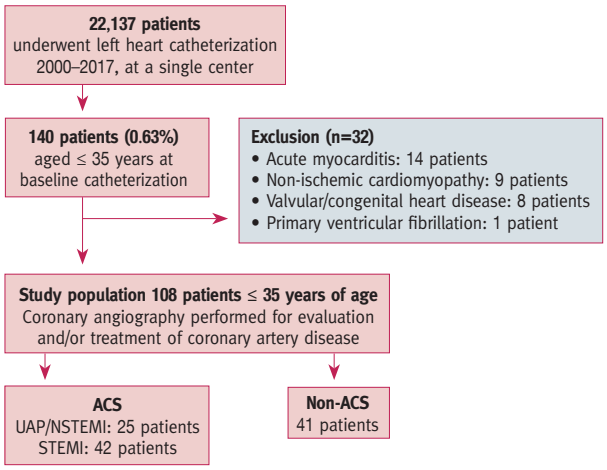
Prevalence of traditional cardiovascular risk factors was compared to older age groups (45–55 and 56–65 years) of patients referred to their first cardiac catheterization performed for the assessment and/or treatment of CAD at the same cardiac catheterization laboratory, in a similar time period.

### DATA ANALYSIS

Continuous data are presented as means ± standard deviation and categorical variables as numbers and percentages. Independent samples *t*-test was used to compare continuous variables and chi-square compared categorical variables. Fisher's exact test was used in cases of small numbers. Long-term outcomes were calculated using the Kaplan–Meier method, and statistical comparison was performed using the log-rank test. Multivariate analysis of the association of FH with long-term coronary revascularization or myocardial infarction was performed using the Cox proportional hazards model with forward stepwise selection of covariates as well as calculating hazard ratios (HR) and 95% confidence intervals (95%CI).

The results were considered statistically significant when the 2-sided *P* value was < 0.05. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA) and MEDCALC version 16.8.4 (MedCalc Software, Belgium). The study was approved by the Carmel Medical Center ethics committee. The need for individual patient consent was waved.

**Figure 1.** Study population flowchart




ACS = acute coronary syndrome, NSTEMI = non ST-segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction, UAP = unstable angina pectoris

## RESULTS

Out of 22,137 patients undergoing left heart catheterizations from 2000 to 2017 at a single center, coronary angiography was performed in 140 patients aged ≤ 35 years (0.63%). Excluded from the current analysis were 32 patients with a discharge diagnosis not associated with CAD. The study flowchart is presented in Figure 1. The final study population included 108 patients aged 35 years or younger who underwent coronary angiography for evaluation and/or treatment of CAD. Of these, 67 presented with ACS (25 UAP/NSTEMI; 42 STEMI) and 41 with non-ACS. STEMI was anterior in 19 patients and inferior or lateral in 23. Mean age was 32 ± 3 years and 88% were males. Major cardiovascular risk factors were similar between the ACS and non-ACS groups [Table 1] and included dyslipidemia (69%), positive family history (64%), current smoking (61%), obesity (39%), hypertension (32%), diabetes (22%), and renal failure (6%). The majority of the population (92%) had at least one conventional risk factor. Significant lipid abnormalities included low high-density lipoprotein (HDL) cholesterol levels ≤ 30 mg/dl in 27 patients (25%), high LDL cholesterol levels > 190 mg/dl in 18 (17%), and severe hypertriglyceridemia > 500 mg/dl in 6 patients (5.5%). Compared to older age groups (45–55 and 56–65 years) undergoing their first coronary angiography for evaluation and/or treatment of CAD, the most notable differences in risk profile of young patients (≤ 35 years) were higher rates of active smoking, positive family history of premature ASCVD, and male gender, in contrast to lower rates of hypertension and diabetes [Table 2].

Eight of the ACS patients (12%) and 29 of the non-ACS patients (71%) had normal epicardial coronary arteries on angiography. These patients did not have any future cardiac

**Table 1.** Cardioavscular risk profile of patients undergoing coronary angiography with ACS compared to non-ACS

| Variable | Total (n=108) | Non-ACS (n=41) | ACS (n=67) | *P* value* |
|---|---|---|---|---|
| Age | 31.8 ± 3.1 | 32.4 ± 2.4 | 31.5 ± 3.3 | 0.112 |
| Gender, male (%) | 95 (88) | 37 (90) | 58 (87) | 0.763 |
| Family history of premature ASCVD (%) | 69 (64) | 25 (61) | 44 (66) | 0.682 |
| Dyslipidemia(%) | 74 (69) | 27 (66) | 47 (70) | 0.674 |
| Hypertension (%) | 35 (32) | 13(32) | 22 (33) | 0.903 |
| Diabetes mellitus (%) | 24 (22) | 8 (20) | 16 (24) | 0.642 |
| Obesity (BMI › 30 kg/m2) (%) | 42 (39) | 14 (34) | 28 (42) | 0.542 |
| Current smoker (%) | 66 (61) | 22 (54) | 44 (66) | 0.229 |
| Chronic kidney disease (%) | 6 (6) | 1 (2) | 5 (7) | 0.405 |
| Total cholesterol, mg/dl | 216 ± 69 | 213 ± 64 | 218 ± 72 | 0.765 |
| Triglycerides, mg/dl | 210 ± 185 | 196 ± 147 | 219 ± 206 | 0.530 |
| HDL cholesterol, mg/dl | 37 ± 11 | 38 ± 10 | 37 ± 12 | 0.754 |
| Peak LDL cholesterol, mg/dl | 174 ± 66 | 163 ± 75 | 182 ± 76 | 0.217 |

*non-significant *P* value for all comparisons

ACS = acute coronary disease, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein

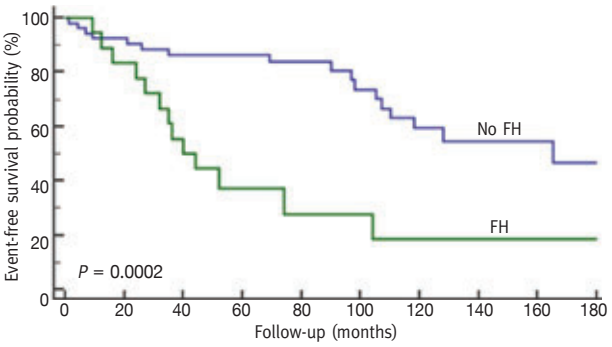
**Table 2.** Comparison of cardioavscular risk factors of patients undergoing a first coronary angiography for evaluation and/or treatment of coronary artery disease at different age groups

| | Age group, years | | | |
|---|---|---|---|---|
| Variable | ≤ 35 (n=108) | 45–55 (n=1695) | 56–65 (n=2556) | *P* value |
| **Gender, male (%)** | 95 (88) | 1,300 (77) | 1,843 (72) | ‹ 0.001 |
| Family history of premature ASCVD (%) | 69 (64) | 528 (31) | 510 (20) | ‹ 0.001 |
| Dyslipidemia (%) | 74 (69) | 942 (56) | 1,589 (62) | 0.003 |
| Hypertension (%) | 35 (32) | 810 (48) | 1563 (61) | ‹ 0.001 |
| Diabetes mellitus (%) | 24 (22) | 437 (26) | 865 (34) | ‹ 0.001 |
| Obesity (BMI › 30 kg/m2) (%) | 42 (39) | 608 (36) | 846 (33) | ‹ 0.001 |
| Current smoker (%) | 66 (61) | 716 (42) | 641 (25) | ‹ 0.001 |

ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index

events (revascularization or myocardial infarction) during long-term follow-up. However, patients with angiographic evidence of CAD (n=71) had adverse long-term outcomes. Revascularization was required in 31 patients (44%) and 23 (32%) presented with myocardial infarction. Six patients (8.5%) died during follow-up, two in-hospital deaths following acute myocardial infarction and four out-of-hospital deaths. Adverse outcomes during long-term follow-up of patients with CAD did not differ significantly in those with primary presentation of ACS and non-ACS: coronary revascularization (41% vs. 58%, $P = 0.343$), myocardial infarction (32% vs. 33%, $P = 0.939$), and all-cause death (8.5% vs. 8.3%, $P = 0.987$), respectively.

**Figure 2.** Myocardial infarction or revascularization during follow-up in coronary artery disease patients with versus without familial hypercholesterolemia




Number at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FH 0 | 53 | 47 | 41 | 36 | 28 | 21 | 15 | 11 | 7 | 3 |
| FH 1 | 18 | 15 | 9 | 4 | 3 | 3 | 2 | 2 | 2 | 2 |

FH = familial hypercholesterolemia

No known cases of cocaine abuse or spontaneous coronary dissection were documented in the current cohort. Thrombophilia or hypercoagulable state was identified in four patients. Two patients had very high lipoprotein(a) levels (known to be associated with atherothrombotic risk) and one patient was diagnosed with vasculitis.

Probable/definite FH according to DLCN criteria was evident in 18 (25%) of the 71 patients with angiographic evidence of CAD. Mean peak LDL-C levels of FH compared to non-FH individuals with CAD was 305 ± 78 mg/dl vs. 148 ± 30 mg/dl, respectively, $P < 0.001$. Multi-vessel coronary disease involvement was observed in all FH patients and in 55% of the non-FH individuals with CAD. Throughout follow-up, coronary artery bypass grafting (CABG) was performed in 10 FH (55%) and 6 non-FH (11%) patients, $P < 0.001$. Furthermore, FH was associated with significantly higher rates of future myocardial infarction or need for revascularization during follow-up [Figure 2]. After adjustment for age, gender, obesity, smoking, hypertension, and diabetes, the hazard ratio for revascularization during long-term follow-up in FH patients was 4.30, 95%CI 2.01–9.18, $P < 0.001$ and for myocardial infarction 2.62, 95%CI 1.15–5.99, $P = 0.022$, compared to the non-FH population with CAD. Similar death rates were noted in both groups during follow-up (6% vs. 9%, $P = 0.609$).

LDL cholesterol treatment goal ≤ 100 mg/dl was achieved by 48% and LDL cholesterol ≤ 70 mg/dl by 17% of the patients with CAD. Attainment rate of cholesterol treatment goals was significantly lower in the FH compared to non-FH population (21% versus 55% reached LDL-C < 100 mg/dl, respectively, $P < 0.001$).

## DISCUSSION

Young adults undergoing coronary angiography for evaluation or treatment of CAD were predominantly male with high

burdens of traditional cardiovascular risk factors, particularly dyslipidemia, active smoking, and a positive family history of premature atherosclerotic cardiovascular disease. Rates of obesity and diabetes were also high considering the young age group. While angiographic evidence of normal epicardial coronary arteries was not associated with any future cardiac events during long-term follow-up, the presence of CAD predicted high rates of revascularization and myocardial infarction in patients with both ACS and non-ACS presentations, especially in FH patients in whom a high burden of atherosclerosis was observed and low rates of lipid treatment goals, were attained.

Clinical CAD is generally uncommon in young adults, as seen in the current analysis, although it should be noted that significant ethnic and geographical disparities exist. For example, compared to Western societies, coronary atherosclerosis tends to present at a younger age and to be more extensive in individuals from the Indian subcontinent [7]. Nevertheless, young patients with CAD represent an important population that is projected to have long-term morbidity with potential psychosocial stressors that may impact on their productivity in society. This young age group with CAD also has the most productive life years to gain from risk factor modification and preventive measures, in light of both their young age and the high burden of traditional cardiovascular risk factors observed.

As was shown in the landmark INTERHEART study across 52 countries, conventional, potentially modifiable risk factors, account for most of the risk of myocardial infarctions worldwide, in all regions [8]. Data from large randomized trials show that most patients with CAD have conventional risk factors [9]. Even among individuals with high genetic risk, a favorable lifestyle was shown to be associated with a nearly 50% lower relative risk of CAD than was an unfavorable lifestyle [10]. Addressing and reversing treatable risk factors in this younger segment of the population with CAD may have particular benefit in reducing their future burden of cardiovascular disease.

A high prevalence of normal coronary angiography in young patients suspected to have CAD is repeatedly observed [11]. Indeed in non-ACS presentations with normal coronary angiography epicardial CAD may never have been present. However, in those presenting with ACS and a normal angiogram, especially when other etiologies mimicking myocardial infarction such as acute myocarditis are excluded, the most likely mechanisms suggested is a totally lysed intra-coronary thrombus or a long-lasting vasospasm of a coronary artery [12]. Smoking, which was highly prevalent in our young cohort, may have predisposed to vasospasm in some of the patients presenting with normal epicardial coronary arteries [13].

The current study is a retrospective analysis; therefore, no systematic study-based effort to identify secondary etiologies for ACS and factors associated with non-atheromatous CAD or myocardial infarction with normal epicardial coronary arteries was possible, but six patients were found to have a hypercoagulable or hyper-thrombotic state and one presented with vasculitis. Autoimmunity may also play an important role in atherosclerotic plaque formation and progression in the young population with CAD [14]. In addition, routine testing for coronary spasm was not performed. Nevertheless, these patients had an uneventful long-term prognosis, which does not support other important additional etiologies as predisposing factors.

Although unreported factors such as thrombophilia, hyperhomocysteinemia, and high lipoprotein(a) levels may have contributed to the atherothrombotic process in a minority of individuals with CAD. It is probable that angiographically visible CAD was mostly driven by the cumulative burden of conventional cardiovascular risk factors observed at an early age. Smoking is highly prevalent in cohorts of young patients with CAD and parental history of coronary heart disease is consistently associated with a higher risk for the development of CAD independent of other established risk factors [15]. Our findings showed that both of these factors are particularly prevalent in the very young population ≤ 35 years of age compared to older age groups evaluated for premature CAD. In addition, dyslipidemia was common in all age groups and is an important risk factor for the development of CAD.

Acute STEMI was the most common presentation of patients with ACS. A higher proportion of STEMI at a younger age among ACS presentations was demonstrated in previous studies and might be related to plaque instability with large lipid core that is more prone to rupture in the younger population, whereas plaque erosion is particularly common in younger women who were less common in the current study cohort [3,16]. This finding is consistent with the high rates of smoking seen in cohorts of young patients presenting with acute STEMI [17] and may be responsible for endothelial dysfunction, vasoconstriction, and pro-inflammatory changes, which leads to a thrombotic milieu.

Cholesterol is a well-established risk factor for CAD, and LDL cholesterol is the primary therapeutic target in patients with CAD. Remnant cholesterol, present in triglyceride-rich lipoproteins, was also shown to be strongly associated with premature myocardial infarction [18]. In addition, an inverse correlation between HDL cholesterol and CAD was repeatedly observed in multiple cohorts of epidemiological studies and low HDL cholesterol is common in young individuals presenting with ACS, especially in smokers [19]. However, pharmacological intervention trials that have focused on increasing HDL levels have been disappointing and have not, to date, improved cardiovascular outcomes [20]. In addition, recent genetic analyses failed to support a causal role for HDL cholesterol in coronary heart disease [21]. Although hypercholesterolemia is one of the most common and treatable causes of heart disease, FH is vastly underdiagnosed and often presents with a premature coronary event [4]. Even in the acute phase during hospitalization, the clinical diagnosis of FH is commonly overlooked, as treatment with a

high-intensity statin on arrival and the inflammatory effect of ACS often mask the high baseline cholesterol levels. Therefore, reviewing the historical, pre-treatment, documented lipid panels and clarifying the family history of each patient admitted with ACS is important and may facilitate better diagnosis of FH [5].

In the present study a quarter of the young patients with angiographic evidence of CAD were clinically diagnosed with probable/definite FH according to a simple algorithm. Although this prevalence of FH seems high and was not noted in previous small-scale observational studies of young patients with CAD [2], recent data from large studies are consistent with our results. In a large European cohort study of patients with premature ACS (< 55 years of age in men and < 60 in women), the prevalence of probable/definite FH according to DLCN algorithm reached 4.8% [22]. Furthermore, among the coronary patients of the EUROASPIRE IV survey, the prevalence of probable/definite FH according to modified DLCN criteria was 8.3%, reaching 20% under the age of 50 years [23].

The long-term prognosis of our young patients with CAD was not benign. This finding may be due to the burden of cardiovascular risk factors and the high prevalence of FH observed in the present study, which was associated with elevated risk for recurrent cardiovascular complications. A recent study similarly showed that compared to patients without FH, the multivariate adjusted risk of coronary event recurrence after ACS was greater in patients with FH with an adjusted hazard ratio of 3.53 [24]. Overall, our findings reinforce the emerging data reporting high prevalence and adverse prognostic implications of FH in young patients with CAD. Moreover, large gaps in the management of FH were noted with low attainment rates of lipid treatment goals, as was repeatedly observed in recent FH studies, highlighting the need to integrate novel therapies such as Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies and improve the quality of care in FH [25].

Several limitations of this study should be noted. Our study was a retrospective analysis from a single center with a small cohort size due to the nature of the study population. This condition may have resulted in selection bias and may limit the generalizability of the study results. In addition, patients were not systematically investigated for factors that may be involved in the pathogenesis of premature CAD, such as vasospasm or thrombophilia, and therefore their prevalence and significance could not be inferred. Moreover, we did not perform any genetic testing and accordingly some of the clinically diagnosed FH patients might have polygenic hypercholesterolemia but not a monogenic disease; nevertheless, our findings display a high-risk of future cardiovascular events in this young population with severe hypercholesterolemia.

## CONCLUSIONS

The burden of traditional cardiovascular risk factors among young adults undergoing coronary angiography is high. Evidence of CAD is associated with considerable rates of future revascularizations and myocardial infarction in both ACS and non-ACS presentations, particularly manifested in patients with FH in whom CAD is more complex and treatment gaps are most significant. These data emphasize the importance of preventive interventions and addressing cardiovascular risk factors at a young age. Future studies should investigate whether identifying and targeting subclinical atherosclerosis in young individuals at high risk for heart disease, such as FH subjects with parental history of premature CAD, is beneficial.

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## Capsule

### (IL-)2 be or not to be?

Immunological T follicular helper ($T_{FH}$) cells are a subpopulation of $CD4^+$ T cells that support B cell antibody production and the establishment of B cell memory. By contrast, non-$T_{FH}$ cells orchestrate enhanced innate immune cell functions at sites of pathogen encounter. The factors underlying differentiation into a $T_{FH}$ or non-$T_{FH}$ cell remain poorly understood, although there is evidence to suggest that the T cell growth factor interleukin-2 (IL-2) may play a role. Using IL-2 reporter mice, **DiToro** et al. showed that naïve $CD4^+$ T cells that produce IL-2 are fated to become $T_{FH}$ cells, whereas non-producers, which receive IL-2, become non-$T_{FH}$ cells. The $CD4^+$ T cell-fate decision was linked to T cell receptor strength. Only those naïve $CD4^+$ T cells that received the highest T cell receptor signals were able to produce IL-2.

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Eitan Israeli

## Capsule

### A target for medulloblastoma

Medulloblastoma is an aggressive brain tumor that most often arises in children and lacks targeted therapeutic options. The subtypes driven by the sonic hedgehog (SHH) pathway are particularly resistant to current drugs, such as SMO inhibitors, that suppress this pathway. **Purzner** and colleagues found that the kinase CK2 drove SHH signaling in medulloblastoma. CK2 inhibitors blocked the growth of SMO inhibitor-resistant as well as SHH-type human and mouse medulloblastoma cells and markedly extended the survival of tumor-bearing mice. A clinical trial is under way to test a CK2 inhibitor in pediatric patients.

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Eitan Israeli

## Capsule

### A dual-targeting painkiller

Opioids are among the most effective treatments for severe pain. Their pain-relieving effects are mediated by activation of the mu opioid receptor (MOR). Unfortunately, selective MOR agonists induce diverse side effects, including respiratory depression, tolerance, hyperalgesia, and dependence. Recently, activation of the nociceptin/orphanin FQ peptide receptor (NOR) has been reported to enhance MOR agonist-induced analgesia without producing side effects. **Ding** et al. developed a bifunctional MOR/NOR agonist called AT-121, which showed potent analgesic effects in nonhuman primates without inducing hyperalgesia, respiratory depression, or dependence. Bifunctional MOR/NOR agonists thus might represent a safe and effective pharmacological tool for treating severe pain.

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Eitan Israeli

**"If we do not change our direction, we are likely to end up where we are headed"**

Chinese Proverb